REMARKS

Claim Status

Claims 1, 12, 22 and 23 have been amended. Claim 11 has been cancelled. Claim 25 has been added. Claims 1-6 and 8-10, and 12-25 are thus pending in this application.

Claims 1, 12, 22 and 23 have been amended to recite that the anti-tenascin antibodies used in the claimed method of treatment are administered "by intravenous or intra-arterial injection." . Support for these amendments can be found in the specification at page 6, lines 19-21, and at page 7, lines 11-12. Claim 11 has been cancelled. The limitation of claim 11, i.e., parenteral injection of the anti-tenascin antibody, has been incorporated into claim 1 as amended.

New claim 25 recites the method of treating lymphoma according to claim 23, "wherein said antibody is selected from the group consisting of monoclonal antibody ("MAb") 81C6 and antibodies that bind to the epitope bound by monoclonal antibody 81C6." Support for this amendment is found throughout the specification, *e.g.*, at page 2, lines 11-12, and in original claims 4 and 12.

No new matter has been introduced in these amendments. Upon entry of these amendments, claims 1-6, 8-10, and 12-25 will be pending. Entry and consideration of these amendments is respectfully requested.

Rejection of Claims 4, 12-22 and 24 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 4 and 12-22, and 24 under 35 U.S.C. § 112, first paragraph, as failing to provide adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

Applicants continue to respectfully disagree with this assertion.

As previously noted, the present invention is directed to the new use of a **known** compound. In particular, the anti-tenascin monoclonal antibody 81C6 was described in U.S. Patent No. 5,624,659 to Bigner et al. A review of the patent file reveals that a Sequence Listing under 37 C.F.R. §1.821(c) for the nucleotide and amino acid sequences described in the specification was submitted during prosecution of the application. By providing the relevant sequences and the synthesis of specific antibodies for use in the patented invention, one of ordinary skill in the art is provided a repeatable method for obtaining the 81C6 antibody. Accordingly, since the present invention is directed to a new use of this compound, Applicants respectfully submit that a deposit of the hybridoma that produces the molecule designated as antibody 81C6 for patent purposes is not required in this instance where the cell lines can be reproduced without "undue" experimentation.

Accordingly, Applicants respectfully submit that Claims 4 and 12-24 comply with the written description requirement and the enablement requirement of 35 U.S.C. §112, first paragraph, and Applicants respectfully request withdrawal of these rejections.

However, in order to expedite prosecution, Applicants are willing to deposit the hybridoma that produces the molecule designated as antibody 81C6 in a recognized depository, once the Examiner has indicated that the present claims are otherwise in condition for allowance. Once the deposit has occurred, Applicants will provide the U.S. PTO with a verified statement corroborating that the deposit was made.

Rejection of Claims 1-6, 8-22, 23 and 24 Under 35 U.S.C. § 103(a) -- Obviousness

Claims 1-6, and 8-24 stand rejected for obviousness over the U.S. Patent 5,624,659 (Bigner et al.; "*Method of treating brain tumors expressing tenascin*") (the '659 patent), in view of Rizzieri

et al., "*Markers of Angiogenesis, Factor VIII and Tenascin, Correlate with Disease Activity in Patients with Non-Hodgkin's Lymphoma*" Abstract #4339, Blood, vol. 94(10), part 2, supplement 1, p. 4339 (1999) ("*Rizzieri 1999*").

The Examiner states that the '659 patent teaches methods of treating solid and cystic tumors using the radiolabeled monoclonal antibody 81C6. The Examiner acknowledges that '659 does not teach a method of treating lymphomas, but asserts that *Rizzieri 1999* teaches that expression of tenascin is elevated in Non-Hodgkins Lymphoma patients. The Examiner asserts that it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the claimed invention to treat lymphomas with the therapeutic monoclonal antibody of the '659 patent. In addition, according to the Examiner, one of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success, because the '659 patent teaches that any tumor that expresses tenascin could be treated with the therapeutic MAb 81C6 and *Rizzieri 1999* states that "the increase in tenascin expression [in Non-Hodgkin's lymphomas] suggests systemically delivered anti-tenascin antibody may be an effective form of therapy."

Applicants respectively disagree and assert that the pending claims, as amended, would not have been obvious.

For a claim to be obvious under 35 U.S.C. § 103(a), three criteria must be satisfied:

1. there must be some suggestion or motivation to combine or modify the cited references;
2. there must be a reasonable expectation of success of combining or modifying the cited references; and
3. the combined references must teach each and every limitation of the claimed invention.

Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000).

A *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

Also, rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (*in banc*).

In addition, it is well established law that the proposed combination cannot render the prior art unsatisfactory for its intended purpose. *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984) and MPEP 2143.01. If the proposed combination of references would change the principle of operation of the prior art invention being modified, then the references are not sufficient to render the claims obvious (*In re Ratti*, 270 F.2d 819 (CCPA 1959); MPEP 2143.01).

A. The '659 Patent Teaches Away from the Claimed Invention

The current claims, as amended, call for "a method of treating lymphoma by administering *intravenously* or *intra-arterially*" an antibody that binds to tenascin. Conversely, the method according to the '659 patent requires *depositing the antibody directly* into the cyst cavity of a cystic tumor or, in the case of solid tumors, *depositing the antibody directly* into a resection cavity, in order to be successful.

The specification of the '659 patent discloses that "the possibility of utilizing therapeutic antibodies in the treatment of cancer is beginning to be investigated ... [but that] satisfactory treatments are not yet available." (Col. 1, lines 37 - 47). In order to develop such a satisfactory treatment, the '659 inventors moved away from classical treatment methods that

involved systemic administration, *e.g.*, intravenous or intra-arterial injection, of therapeutic antibodies and turned instead to methods that involved *depositing the antibody directly* into the cyst cavity of a cystic tumor ('659 patent, col. 1, lines 49-57) or, in the case of solid tumors, *depositing the antibody directly* into a resection cavity that results after surgery to remove the tumor ('659 patent, col. 1, line 58 - col. 2, line 2). The rationale behind this novel treatment method was that systemic administration of MAb 81C6 simply was not suitable for treating brain cancers.

Indeed, as noted during a October 25, 2005 telephonic interview between Examiner Alana M. Harris, Ph.D. and Drs. Darell Bigner, Michael Zalutsky and David Rizzieri (Drs. Bigner, Zalutsky and Rizzieri are named inventors in the instant patent application, and Drs. Bigner and Zalutsky are co-inventors on the '659 patent and Dr. Rizzieri is the first-named author of *Rizzieri 1999*), Drs. Bigner and Zalutsky attempted to develop a treatment for brain cancer that utilized monoclonal antibody 81C6 administered by intravenous or carotid artery injection. Drs. Bigner and Zalutsky found that they were not able to achieve or maintain *therapeutically effective levels* of the delivered isotope at the desired tumor target. The literature bears this out. For instance, see Bigner et al. "*Iodine-131-Labeled Antitenascin Monoclonal Antibody 81C6 Treatment of Patients With Recurrent Malignant Glioma: Phase I Trial Results*" (Journal of Clinical Oncology **16**:2202-2212 (1998) (*Bigner 1998*); attached as **Exhibit 1**), in which the authors, including the aforementioned Drs. Bigner and Zalutsky, state "However, *systemic administered* radiolabeled mAbs [monoclonal antibodies] do not accumulate in primary CNS neoplasm in amounts sufficient to deliver therapeutic levels of radiation without significant systemic toxicity." (*Bigner 1998*, page 2202, column 2, first full paragraph). *Bigner 1998* cited two articles published previously (again, by Drs. Bigner and Zalutsky et al.) in support of this statement: 1) Zalutsky et al. "*Pharmacokinetics and tumor localization of 131I-labeled anti-tenascin monoclonal antibody 81C6 in patients with gliomas and other intracranial malignancies*" (Cancer Res. **49**:2807-2813 (1989) (*Zaklutsky 1989*; attached as **Exhibit 2**); and 2) Zalutsky et al., "Monoclonal antibody and

F(ab')2 fragment delivery to tumor in patients with glioma: comparison of intracartoid and intravenous administration" (Cancer Res. **50**:4105-4110 (1990) (*Zaklutsky 1990*; attached as **Exhibit 3**). *Zaklutsky 1989* showed that tumor uptake after intravenous injection was antibody specific but that it was also too low to be used for therapy. *See Zaklutsky 1989*, page 2811, col. 2. And *Zaklutsky 1990* showed intra-arterial injection did not significantly increase tumor uptake (compared to intravenous injection) in brain tumor patients. *See Zaklutsky 1990*, page 4109, col. 2.

The Examiner points to the '659 patent at col. 3, line 20 - col. 4, in support of her assertion that the radiolabeled MAb 81C6 disclosed in the '569 patent can be "used in the treatment of any tumor that expresses tenascin." (March 10, 2007 Office Action, page 6, lines 6-10). Applicants wish to point out that the success of the cancer treatment depends on the method of administration of the antibody. The '659 patent does not teach only that MAb 81C6 may be used to treat any tumor that expresses tenascin. Rather, the '659 patent teaches that the method disclosed may be used in treatments involving MAb 81C6. *See* the '659 patent col. 3, lines 65-67. One of ordinary skill in the art might indeed be motivated to treat lymphomas with the therapeutic monoclonal antibody of the '659 patent, but would only have a reasonable expectation of success if the antibody was *deposited directly in the tumor*. In fact, based on the *Bigner 1998* disclosure, one of ordinary skill in the art at the time of the invention would *not have had any* expectation of success when attempting to treat any tumor that expresses tenascin systemically administering an anti-tenascin antibody.

Moreover, as indicated above the proposed combination cannot render the prior art unsatisfactory for its intended purpose. *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984) and MPEP 2143.01. If the proposed combination of the references would change the principle of operation of the prior art invention being modified, then the references are not sufficient to render the claims obvious (*In re Ratti*, 270 F.2d 819; MPEP 2143.01). As demonstrated above, the use of *Rizzieri 1999*'s

method of systemic administration would have rendered the '659 invention unsuitable for successfully treating brain cancer.

Thus, the "combined teachings" of the cited references were shown to be unsuccessful in treating brain tumors as discussed above. Therefore, the combination of the cited references would not enable one of ordinary skill in the art to arrive at the present invention directed to methods of treating lymphoma by administering a radiolabeled anti-tenascin monoclonal antibody intravenously or intra-arterially.

Accordingly, Applicants respectfully submit that claims 1-6, 8-10 and 12-24, as amended, are not obvious under 35 U.S.C. § 103(a) in view of the '659 patent in combination with *Rizzieri 1999*, and Applicants respectfully request withdrawal of these rejections.

B. The Claimed Invention Yields Unexpected and Improved Results

As stated above, a *prima facie* case of obviousness may also be rebutted by showing that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (*in banc*). Also, as stated in the Manual of Patent Examining Procedure (M.P.E.P.), "Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage." M.P.E.P. §716.02(a) (citing *Ex parte The NutraSweet* Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991)).

As shown above, one of ordinary skill in the art would not have any expectation of success when treating any cancer exemplified by tumors that express tenascin by injecting an anti-tenascin antibody either intravenously or intra-arterially.

In addition, in a December 8, 2005 Amendment in this case, Applicants set forth other arguments that the claimed method yields unexpected results, based on statements made in a October 7, 2004 Declaration by inventor David A. Rizzieri, namely 1) the rapid uptake of ^{131}I anti-tenascin chimeric 81C6 monoclonal antibody in the liver and marrow and a slower and enhanced uptake in selected tumor sites as opposed to normal organs; (2) at least 2-fold greater retention of the radiolabeled antibody in lymphomas as compared to normal tissue; (3) the estimated average absorbed dose to selected tumors of ^{131}I anti-tenascin chimeric 81C6 monoclonal antibody was higher than that obtained from ^{131}I-tositumomab (tositumomab (Bexxar®) is a commercially available labeled antibody for treatment of lymphoma); and (4) the instant radiation dose delivered to the tumor per unit of administered activity was higher than that seen with ^{131}I-tositumomab and consequently these results indicate substantially longer tumor retention than reported for other antibodies evaluated for radioimmunotherapy (tositumomab, anti-CEA hMN-14, anti-TAG72 CC49, A33,17-1A, for example).

The Examiner has rejected applicants' assertion that the claimed method yields unexpected results, contending that applicants' comparison of a radiolabeled anti-tenascin antibody with other radiolabeled antibodies fails because it is predicated on antibodies that are structurally different, bind different targets, and have different absorption rates and tumoricidal activities.

Applicants respectfully disagree. These arguments were not put forth because Applicants were attempting to demonstrate that the 81C6 monoclonal antibody was a better antibody than those in the prior art. Rather, they were used to demonstrate that the claimed method of radiolabeled antibody-facilitated therapy targeted to tenascin is far superior than other methods employing the above-mentioned antibodies. Taken in the proper context, the information above demonstrates that the claimed method of treating lymphomas by intravenous or intra-arterial administration of a radiolabeled anti-tenascin monoclonal antibody yields significant, unexpected, and unobvious results. All of the above-mentioned antibodies are specific for cell surface antigens. Tenascin, on

the other hand, is an extracellular matrix protein expressed in tumor stroma. The methods according to this invention represent the first intravenous use of a radiolabeled antibody directed toward a stromal target. *See Rizzieri* et al., "*Phase I Trial study of ^{131}I-labeled chimeric 81C6 monoclonal antibody for the treatment of patients with non-Hodgkin's lymphoma*" page 642, columns 1 and 2 (Clinical Observations, Interventions, And Therapeutic Trials **104**:642-648 (2004) (*Rizzieri 2004*, attached as **Exhibit 4**). Based on the negative results when ^{131}I-labeled anti-tenascin MAb 81C6 was evaluated for systemic administration for treating brain cancer, and considering that the claimed method of treating lymphoma represents pioneering work, it was completely unexpected that intravenous administration of radiolabeled MAb81C6 resulted in enhanced uptake in selected tumor sites as opposed to normal organs and at least 2-fold greater retention of the radiolabeled antibody in lymphomas as compared to normal tissue, and also that therapeutic levels of radiation were absorbed better than ^{131}I-tositumomab and retained longer than reported for tositumomab and other antibodies evaluated for radioimmunotherapy. This represents a significant practical advantage other methods of treating lymphomas, because target uptake and retention are critical components of successful therapy employing radiolabeled antibodies.

Accordingly, at least in view of these unexpected results clearly presenting a significant and practical advantage, Applicants respectfully submit that claims 1-6, 8-10 and 12-24, as amended, are not obvious under 35 U.S.C. § 103(a) in view of the '659 patent in combination with *Rizzieri 1999*, and Applicants respectfully request withdrawal of these rejections.

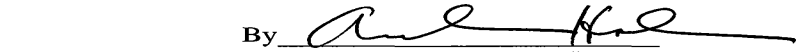
B. New Claim 25 is Not Obvious

New claim 25 recites the method of claim 23, wherein the antibody employed in the method is selected from the group consisting of monoclonal antibody 81C6 and antibodies that bind to the epitope bound by monoclonal antibody 81C6. For the same reasons as stated above for claims 1-6, 8-10, and 12-24, new claim 25 is not obvious.

In view of the above amendments and remarks, the pending claims are believed to be in condition for allowance and such action is earnestly solicited. The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of the pending claims to issue. In any event, any questions that the Examiner may have should be directed to the undersigned, who may be reached at (212) 527-7608.

Dated: May 19, 2006

Respectfully submitted,

By 

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